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UNIVERSITÀ DEGLI STUDI DI TORINO

Editorial

Role and function of exosomal miR-9-3p in hepatocellular carcinoma

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MicroRNAs (miRNAs) are small (~20-22 nucleotides) non-coding RNAs able to regulate gene expression through repression or degradation of mRNAs.[1] MiRNAs are the biggest class of genetic regulators and they act at a post-transcriptional level with a mechanism based on sequence complementarities between miRNA and target messenger RNA (mRNA) (Figure 1).[2] MiRNAs are important regulator of the principal cell functions including growth, proliferation, differentiation and apoptosis, being involved in the oncogenic processes acting as oncogenes, tumor suppressor genes or both.[3] In addition, there is a growing interest to explore circulating miRNAs as potential biomarkers for early hepatocellular carcinoma (HCC) detection.[4]

Sun *et al*. observed an increased expression of miR-9 (*i.e.* miR-9-5p) in HCC tissue compared to normal liver and adjacent non-cancerous tissues; higher miR-9 expression was associated with a poor prognosis of HCC.[5] Furthermore, it has been reported that miR-9 could promote tumour cell migration and invasion in HCC cell lines.[6]

Recently, Tang *et al* investigated the biological function of exosomal miR-9-3p (the "minor" product of miR-9) with a focus on its involvement in the proliferation of HCC cells.[7] Interestingly, in an experimental model authors observed that miR-9-3p, as miR-9, is overexpressed in HCC cell lines, but showing opposite biological effects. Indeed, miR-9-3p was able to inhibit HCC cells proliferation by directly suppressing heparin-binding growth factor-5 (*HBGF-5*) expression, a gene member of the fibroblast growth factor (FGF) family,[8] and by inhibiting the extracellular signal-regulated protein kinase 1 and 2 (*ERK1/2*) expression, involved in the regulation mechanism of cell proliferation and apoptosis.[9]

In addition, Tang *et al* found that miR-9-3p levels were significantly higher in the serum exosomes of normal donors compared to patients with HCC. The accuracy for the discrimination between donors and HCC patients was 0.813 (area under the curve) indicating a good diagnostic performance for miR-9-3p.[7] To date, several studies assessed the potential role of miRNAs as well as other classes of biomarkers for HCC detection and reported promising results.[1, 10-13] However,

must be stressed that caution should be used when dealing with miRNAs and other epigenetic molecules,[14, 15] since the complex miRNA-mRNA interaction may be affected by numerous other genetic and epigenetic features, consequently resulting in an alteration of miRNAs expression.[16] In addition, the use of such molecules as cancer biomarkers is partly limited by lack of standardized method for their quantitation. Since there is still a need of reliable biomarkers for HCC detection, the use of traditional biomarkers assessed by novel highly sensitive and fully automated analytical methods, may be the most effective strategy to address this clinically relevant issue.

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Figure 1.-Biogenesis and function of miRNAs.

MiRNAs are transcribed in the nucleus by RNA polymerase II as a stem-loop primary transcript (pri-miRNAs). Following a cleavage by the ribonuocleoprotein complex Drosha/DGCR8, hairpin precursor-miRNAs (pre-miRNAs) are exported into the cytoplasm through exportin-5. Then, pre-miRNAs are further processed by another RNAse III (Dicer) into an RNA-duplex consisting of the mature miRNA and the passenger miRNA strand. Subsequently, miRNA duplex is unwinded by helicase activity and the mature miRNA (arisen from the 5' arm) can be incorporated into the RNA-induced silencing complex (RISC). Usually, the "minor" passenger strand (arisen from the 3' arm) is not functional and cannot be incorporated into the RISC complex. The miRNA-RISC complex allow the interaction between the mature miRNA and the target mRNA. According to miRNA-mRNA complementarity, their interaction induces either mRNA translation repression or mRNA degradation.

Abbreviations: miRNA, microRNA; RISC, RNA-induced silencing complex.